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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,297	08/24/2005	Joseph Alexander Lasky	ON/4-32744A	1063

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EXAMINER	
THOMAS, TIMOTHY P	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,297	LASKY, JOSEPH ALEXANDER	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,5,7 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,5,7 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicants' arguments, filed 9/27/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. Applicant's arguments with respect to the rejection of claims 2 and 10 under 35 USC 103 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 4 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims depend on claims which have been canceled; therefore the subject matter of these claims is indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 10, 2, and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pulmonary hypertension in the sense

of the meaning of reduction of pulmonary hypertension in individuals with pulmonary hypertension, does not reasonably provide enablement for treating individuals in the sense of the meaning of curative or prophylactic treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant has given a special meaning to the term "treating" that includes curative and prophylactic treatment (specification p. 5, 3rd-5th paragraphs). While applicant has enabled a method of treating pulmonary hypertension, in the sense of the meaning of reducing the pulmonary blood pressure in individuals with pulmonary hypertension, curing and preventing the disease are not considered enabled.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method of treating humans suffering from pulmonary hypertension which comprises administering to a said human in need of such treatment

a dose effective against pulmonary hypertension of imatinib (the compound of formula (I)) or a pharmaceutically acceptable salt thereof, wherein a daily dose of 100-1000 mg is administered. Thus, the claims taken together with the specification imply administering a 100-100 mg dose of imatinib will 1) prevent pulmonary hypertension from developing and 2) will cure pulmonary hypertension in an individual that has pulmonary hypertension.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Fukumoto, et al. ("Recent Progress in the Treatment of Pulmonary Arterial Hypertension: Expectation for Rho-Kinase Inhibitors"; 2007; Tohoku Journal of Experimental Medicine; 211: 309-320) teaches pulmonary arterial hypertension (PAH) is a disease with poor prognosis characterized by progressive elevation of pulmonary arterial pressure and vascular resistance due to pulmonary hyperconstriction and remodeling; the precise mechanism still remains to be elucidated (abstract); although anticoagulant agents, vasodilators and lung transplantation are currently used in the treatment of PAH, more effective treatment needs to be developed (abstract; p. 317, right 3rd paragraph); the WHO classification of pulmonary hypertension is divided into 5 categories with multiple disease listings in each of these categories (p. 310, Table 1), and Figure 1 (p. 312) shows "unknown triggers at the top of the illustration of pathophysiological components contributing to the development of pulmonary hypertension. These characteristics demonstrate the diversity and complexity of pulmonary hypertension as a group of diseases, and suggest that a treatment to cure and prevent the diseases would be unpredictable

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for an 80% reduction of pulmonary hypertension in rats that had been exposed to hypobaric-hypoxic conditions.

However, the specification does not provide examples nor reasoning that would support the claim to prevent or cure pulmonary hypertension.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the many related diseases that are considered pulmonary hypertension, the current poor prognosis in patients, the precise mechanism by which pulmonary arterial pressure is elevated is unknown and the disease is initiated by unknown triggers and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Claim Rejections - 35 USC § 103

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Claims 10, 2 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goncharova, et al. ("PI3K is required for proliferation and migration of human

pulmonary vascular smooth muscle cells"; 2002 Mar 8; Am. J. Physiol. Lung Cell. Mol. Physiol.; 283: L354-L363); Tanabe, et al. ("Mechanical stretch augments PDGF receptor β expression and protein tyrosine phosphorylation in pulmonary artery tissue and smooth muscle cells"; 2000; Molecular and Cellular Biochemistry; 215: 103-113); and Zimmermann, et al. (WO 99/03854 A1; 1999; IDS 4/21/2005 reference AM).

Goncharova teaches human vascular smooth muscle cell proliferation and migration contribute to vascular remodeling in pulmonary hypertension and atherscerosis; that stimulation of human pulmonary vascular smooth muscle (PVSM) with platelet derived growth factor (PDGF) induced PI3K-dependent activation of Akt, p70 S6 kinase and ribosomal protein S6; and that PDGF-induced proliferation and migration was inhibited by LY-294002 (a kinase inhibitor; abstract); PDGF appears to be the most potent activator of the PI3K singnaling pathway in many cell types (p. L360, last paragraph); regulation of cell proliferation and motility is a critical step in vascular remodeling, and suggests that targeting PI3K-dependent human PVSM cell motility and proliferation may offer a potential target in blocking development of lesions in atherosclerosis and hypertension (p. L362, last paragraph). Tanabe teaches mechanical stretch of pulmonary artery tissue identified tyrosine phosphorylation proteins that respond to mechanical stress, which included p55 as one of two proteins preferentially phosphorylated by stretch in endothelial cells, corresponding to PDGF receptor β; significant increase in RNA level for PDGF-Rβ was observed in the pulmonary artery of rats with induced pulmonary hypertension, suggesting that stretch-induced overexpression of cell-surface PDGF-Rβ as well as augmentation of tyrosine

phosphorylation of proteins might be involved in the mechanotransduction of pulmonary artery (abstract); mechanical stimulus such as stretch induces several responses including smooth muscle contraction, proliferation and apoptosis (p. 103, 1st paragraph); and an inhibitor of tyrosine kinase specifically suppressed the pressure-induced contraction of rat cerebral artery (p. 104, 2nd paragraph).

Neither Goncharova nor Tanabe teach the compounds of the instant claims, nor a method of treating pulmonary hypertension with one of these compounds. Zimmerman teaches the compound of instant formula (I) (imatinib or STI571; abstract) and the monomethanesulfonic acid salt of imatinib (p. 4, figure (II)); phosphorolation of proteins has long been known as an essential step in the differentiation and division of cells, a process catalyzed by protein kinases, including the tyrosine kinase PDGF receptor; this growth factor plays an important role in normal growth and in pathological cell proliferation, such as in carcinogenesis and in diseases of the smooth-muscle cells of blood vessels, such as in artherosclerosis and thrombosis (p. 9, last 3 paragraphs); the compounds imatinib and its methanesulfonic acid salt are active in inhibition of PDGF receptor kinase and as inhibitors of several kinases (p. 11); the compounds are useful in treatment of cancers and non-malignant diseases, such as artherosclerosis and fibrosis (p. 11, 1st paragraph), and leukemias including chronic myeloid leukemia (p. 11, last paragraph), and diseases with vascular smooth-muscle cell migration and proliferation where PDGR and PDGF-R often play a role, such as restenosis and artherosclerosis; daily dosages include the range of 5-500 mg (p. 17, 1st paragraph), with the specific dosage of 100 mg taught (p. 20, Example 4; p. 21, Example 6).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer an effective dose of imatinib or the monomethanesulfonic acid salt of imatinib in the treatment of pulmonary hypertension. The motivation would have been the following three mechanistic roles for which imatinib is active: 1) both Goncharova and Tanabe implicate the role of PDGF-R in pulmonary hypertension and Zimmerman teaches imatinib is useful in diseases where PDGF-R plays a role; 2) Gocharova teaches cell proliferation and motility is a critical step in vascular remodeling, imatinib inhibits such processes; and 3) Tanabe teaches phosphorylation of PDGF receptor β by stretch in endothelial cells is a component of pulmonary hypertension, such phorsphorylation is inhibited by imatinib. It would not only have been obvious to treat patients with pulmonary hypertension accompanied by pulmonary fibrosis, and also to treat patients before the disease progresses significantly (i.e., before evidence of pulmonary fibrosis is present). The motivation for treating patients early would have been to potentially arrest the progress of the disease so that fibrosis does not occur or is delayed in its onset. It would also have been obvious to treat patients with both primary or secondary pulmonary hypertension with imatinib, considering at least 3 mechanistic reasons existed for such treatment at the time of the invention. It would also have been obvious to treat administer imatinib for a period exceeding three months, since therapies for conditions such as artherosclerosis or hypertension are routinely continued for time periods in excess of three months, Or until the condition remains at normal levels over a period of time on the order of months between visits to a physician.

It is noted that applicant has presented arguments in rebuttal of the previous rejection under 35 USC 103 that pulmonary hypertension is a disease not related to cancer; cancer treatments are a use for which tyrosine kinase inhibitors such as imatinib are well known. Although pulmonary hypertension and cancer are different diseases, it is not accurate that cancer is unrelated to pulmonary hypertension. In fact, Dingli, et al. ("Unexplained Pulmonary Hypertension in Chronic Myeloproliferative Disorders"; 2001; Chest; 120 (3): 801-808) reported a study in which a correlation was observed between pulmonary hypertension and chronic myeloproliferative disorders (that have a propensity to evolve into an acute leukemia, for which imatinib is an established treatment) (abstract; throughout). Although the underlying reasons for this are unknown by Dingli, this study would have supported the concept of imatinib therapy as treatment for pulmonary hypertension for the reasons outlined above.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1614

/Ardin Marschel/
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